REVIEW

Novel human herpesviruses (human herpesviruses 6, 7 and 8)

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The number of members in the family Herpesviridae has increased in the last 10 years due to the description of three novel human herpesviruses: human herpesvirus 6 (HHV-6) in 1986, human herpesvirus 7 (HHV-7) in 1990, and human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), in 1994. HHV-6 and HHV-7 were first isolated from blood lymphocyte cultures, while HHV-8 was identified following a specific molecular biology approach in the search for the etiologic agent of Kaposi's sarcoma. The three viruses are lymphotropic, T-cells being the targets of HHV-6 and HHV-7, and B-cells being probably those of HHV-8. The ability to be propagated in cell cultures in vitro differs according to the virus concerned: this can be done readily with HHV-6, with more difficulties in the case of HHV-7, and has not yet been achieved in the case of HHV-8. Human infection with HHV-6 and HHV-7 is ubiquitous, widespread and acquired early in life. HHV-8 epidemiology is still unclear, and there are two hypotheses: a restricted dissemination in the general population like herpes simplex virus type 2, or a widespread infection like all other human herpesviruses. The polymerase chain reaction is the common method for the detection of infection using specific primers and probes for HHV-6, HHV-7 and HHV-8 respectively. Serologic assays are only available for HHV-6 and HHV-7, with limitations being due, in particular, to possible cross-reactions with cytomegalovirus. HHV-6 is the causative agent of exanthem subitum (sixth disease). Its role as an opportunistic agent and immune dysfunction inducer is debated and currently under investigation. The pathogenic role of HHV-7 seems to be modest, with one case of exanthem subitum reported so far. HHV-8 is strongly associated with three diseases: Kaposi's sarcoma, Castleman's disease and body-cavity-based lymphomas. The therapy against these novel viruses has to be considered in the future.

Key-words: Herpesvirus, T-lymphocyte, B-lymphocyte, PCR, AIDS, Kaposi's sarcoma

Three novel human herpesviruses have emerged in the past 10 years. Until 1986, five viruses of the Herpesviridae family were known to cause infections and induce diseases in humans: herpes simplex viruses 1 and 2 (also called human herpesviruses 1 and 2), varicella-zoster virus (also called human herpesvirus 3), Epstein–Barr virus (also called human herpesvirus 4) and human cytomegalovirus (also called human herpesvirus 5). These five viruses were classified into three subfamilies: herpes simplex viruses (HSV) and varicella-zoster virus (VZV) into the Alphaherpesvirinae subfamily, human cytomegalovirus (CMV) into the Betaherpesvirinae, and Epstein–Barr virus (EBV) into the Gammaherpesvirinae. Like other herpesviruses, these five 'classical' human herpesviruses chronically infect their hosts and are able to induce severe diseases, especially in immunocompromised persons. Infection is ubiquitous and widespread, concerning the majority of the general population, except for HSV2, which is quasi-exclusively transmitted by sexual contact and infects only a minority of the adult population.

Human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7) and human herpesvirus 8 (HHV-8, also known as KSHV for Kaposi's sarcoma-associated herpesvirus) were discovered in 1986, 1990 and 1994 respectively. Their discovery illustrated the value of novel investigation procedures in human virology. These procedures were, in particular, the culture of lymphocytes in vitro thanks to the availability of

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growth factors and the selective amplification of virus genomes using techniques derived from the polymerase chain reaction (PCR). The emergence of HHV-6, HHV-7 and HHV-8 has considerably modified the picture of human virus infections, although numerous questions remain unsolved. Primary characterization has indicated that the three novel herpesviruses share common properties. They all infect lymphocytes and can be detected in the peripheral blood of infected people, within the mononuclear cell fraction. However, they appear to be clearly different from each other, and the amounts of data regarding each of them are very dissimilar. A lot of information has been progressively obtained about HHV-6, while the study of HHV-7 has been comparatively neglected. At present, numerous data are being collected about HHV-8 and tend to obscure the other domains of research on novel herpesviruses. However, major features concerning HHV-8 infection, such as its prevalence in the general population and its route of transmission, are still unknown.

HUMAN HERPESVIRUS 6 (HHV-6)

Virologic properties

HHV-6 was first isolated from cultures of peripheral blood lymphocytes obtained from patients with various lymphoproliferative diseases [1]. The objective of such cultures was the identification of novel human retroviruses. A cytopathic effect was detected, consisting of enlarged refractile cells which were ultimately destroyed [2]. This cytopathic effect could be serially propagated but was not reminiscent of any retrovirus effect and was not associated with any reverse transcriptase activity. Infected cells were shown to contain viral particles exhibiting the morphology of herpesviruses. No reactivity with either nucleic probes or antibodies specific for HSV1, HSV2, VZV, CMV and EBV was observed, which indicated that this human herpesvirus was a novel one. Initially named human B-lymphotropic virus (HBLV) because of an assumed preferential tropism for B-lymphocytes, this virus was later designated officially as HHV-6, when it became obvious that its main tropism was for T-lymphocytes [2,3].

The HHV-6 structure is very similar to that of other herpesviruses [3]. Enveloped virions, about 200 nm in diameter, contain nucleocapsids which are 100 nm in diameter and exhibit icosahedral symmetry. Capsids enclose a core in which the HHV-6 genome is located. This genome is composed of linear double-stranded DNA, approximately 167 kbp long, consisting of a 143-kbp unique region flanked by two identical directly repeated sequences. The complete nucleotide sequence of the HHV-6 genome has recently been obtained [4].

Two major facts have emerged from the genetic analysis of HHV-6. Although this virus is clearly distinct from the five 'classical' human herpesviruses, it is genetically related to CMV, as evidenced both by partial nucleotide sequence homologies and gene block colinearity [4–6]. Recent data indicated that HHV-6 is also very closely related to HHV-7. This has led to the classification of HHV-6 into the Betaherpesvirinae subfamily. Some common phenotypic properties, such as the sensitivity to antivirals in vitro [7] parallel the genetic relationship between HHV-6 and CMV. A second major property is the existence of two groups of viruses within the HHV-6 species. These two groups can be unambiguously distinguished from one another by means of phenotypic properties such as in vitro growth requirements, reactivity with panels of monoclonal antibodies, restriction endonuclease profiles and nucleotide sequencing [8,9]. Following a long debate on the hierarchical level of distinction between these two groups, regarding species, types and subtypes, they are now designated as the variants A and B of HHV-6 [10]. The differences in disease association between variants A and B are less clear than the differences in virologic properties. Variant B is detected in peripheral blood much more frequently than variant A [11], but with respect to pathogeny, the respective roles of the two variants are difficult to assess, especially because mixed infections seem to occur very often [12].

Although CD4 is not the cell receptor for HHV-6 [13], the virus exhibits a marked tropism for CD4-positive T-lymphocytes [2,3]. It can also infect monocyte-macrophages and CD8-positive lymphocytes. Infection of CD8-positive cells with HHV-6 induces the expression of CD4 at the surface of cells, which, in turn, would make these cells susceptible to HIV infection [14]. HHV-6 infection has been obtained experimentally in continuous cell lines of various origins, including T-lymphocytes and megakaryocytic, glial and fibroblastic cells [3]. Generally speaking, adaptation to cell lines may be difficult or impossible in many cases. Primary peripheral or umbilical cord blood mononuclear cells remain the most convenient cells for isolation and serial propagation of most primary HHV-6 isolates. The virus is strongly cell associated and the yield of cell-free virus in culture supernatant is usually low.

Epidemiology

Prevalence studies using serologic assays have shown that HHV-6 infection is ubiquitous and widespread,

being present in most adults in all countries studied so far [3]. Differences of infection frequencies according to different authors reflect differences of sensitivity and specificity between distinct home-made serologic assays rather than high variations of virus dissemination according to geographic areas [15]. Antibody titers tend to decrease with age, which might lead to underestimation of infection rates in adults. Primary infection occurs early in life. The rate of HHV-6-seropositivity and the titer of HHV-6-specific antibodies decrease from birth to 6 months old, corresponding to the loss of maternal antibodies. From 6 months up to 4 years old, the frequency of seropositivity continuously increases, and progressively reaches the level found in the adult population, from 60% up to more than 90% according to different authors [3,15].

Like other human herpesviruses, HHV-6 persists in the host after primary infection. This long-term infection is confirmed by the frequent detection of the virus in both the saliva and blood from healthy people at any age [11,16]. The precise rate of detection varies from one author to another, due to the different sensitivities of the assays used, but the reality of chronic HHV-6 infection is beyond doubt. Virus has been detected in salivary glands, lymph nodes and neurons. Several questions remain unanswered. It is not known whether the virus can stay in a real latent state for a long time or whether an active infection with low virus yields is always present. The preferential site of chronic infection is not precisely known, although blood mononuclear cells (and especially monocytes) and epithelial cells such as salivary gland cells are good candidates. It has been shown that a lot of HHV-6-infected people harbor the two variants of the virus, suggesting the possibility of co-infections or superinfections with two different viruses [12]. It is not known whether reinfections with the same variant can occur. The rate and the circumstances of infection reactivations in chronically infected subjects are not precisely known. Whether these reactivations associated with viremia and, in some cases, increase of antibody titers are frequent or not, chronic HHV-6 infection provides a large reservoir of virus capable of infecting susceptible subjects and maintaining the high rate of infection in the general population.

Virus transmission is probably mediated by saliva in most cases, although a clear demonstration of that route is still missing. Breast milk does not seem to be implicated in transmission. Transmission though blood transfusion has not been reported [17]. Virus has been found in cervical secretion specimens, which might contribute to sexual and perinatal transmission. Intrauterine transmission of HHV-6 has been clearly demonstrated [18]. However, the frequency and the clinical manifestations of congenital HHV-6 infections are not known.

Laboratory methods for diagnosis

HHV-6 is isolated from peripheral blood mononuclear cells and diverse body fluids using lymphocyte culture techniques [3]. The most sensitive cells are primary phytohemagglutinin-stimulated lymphocytes of peripheral or umbilical cord blood obtained from healthy donors. Isolation in primary lymphocyte cultures is a reference method, but its sensitivity for the diagnosis of active HHV-6 infection appears to be limited. During the acute phase of exanthem subitum, isolation rates are above 90%, whereas isolation is much less efficient at the time of reactivations. The detection of virus multiplication in vitro was classically performed by microscopic observation of cytopathic effect [2,3]. The detection of virus antigens and genomes in cultured cells as well as in culture supernatant has been claimed to increase the sensitivity of isolation procedures, in parallel with improvements of culture conditions. However, no standardized highly sensitive method of isolation has been published so far.

HHV-6 can be detected directly without any culture step by means of nucleic acid hybridization, in situ hybridization, PCR and in situ immunohistochemistry. PCR exhibits a high sensitivity, has been widely used, and has permitted us to define semi-quantitative methods using endpoint dilution [18, 19]. This quantitation is of interest with respect to the distinction between 'latent' infection and acute infection or reactivation. Indeed, depending on the sensitivity of the PCR-based method, the rate of detection of HHV-6 DNA in blood cells from healthy people has been found to vary from 5% to more than 90% [16]. In that sense, immunohistochemistry which detects virus antigen expression might be considered a more relevant approach than PCR for the diagnosis of acute infection. For both PCR and immunohistochemistry, special attention must be paid to the capacity of the method to detect either the two variants of HHV-6 or only a single one, according to study objectives. This requires a careful controlled evaluation of primers and probes for PCR, and monoclonal antibodies for immunohistochemistry.

HHV-6 antibodies can be detected using distinct methods, and can be used either for the diagnosis of acute infection or the determination of infection prevalence in a group of subjects. Primary infection is associated with appearance of specific antibodies, including IgM at the beginning of seroconversion, and IgG thereafter. The presence of these specific antibodies is for life, provided that they remain at a detectable level in serum, and their titer does not appear

to be correlated with the occurrence of diseases putatively related to HHV-6. Numerous assays have been described for HHV-6 serology, including immunofluorescence, enzyme-linked immunofluorescence assay (EIA) and neutralization [3]. Neutralization assays are very specific but are time- consuming and not very sensitive. The most widely used test until now has been immunofluorescence, which is much less sensitive than EIA but probably more specific. Specificity is the key question of HHV-6 serology. Cross-reactions have been reported with CMV [20] as well as with HHV-7. This is a major drawback for both diagnosis and prevalence studies of HHV-6 infection. There is no validated variant-specific serologic assay.

Clinical manifestations

It is assumed that most primary HHV-6 infections are asymptomatic. The most common disease associated with primary infection is exanthem subitum, also called roseola infantum or sixth disease [21]. Virus is isolated from blood at the acute phase of the disease; seroconversion with appearance of specific IgM is observed during the convalescent phase. Primary infections are also associated with less typical manifestations such as febrile illness without rash, convulsions, hepatitis and mononucleosis [22–24]. A few fatal cases associated with fulminant hepatitis, meningoencephalitis and disseminated infection have been reported [23,25]. Due to the high prevalence of infection early in life, primary infections of adults seem to be rare but with more severe clinical manifestations than for children.

Clinical manifestations related to chronic infection and reactivations are far more complex [26]. The causative role of HHV-6 in opportunistic infections of immunocompromised subjects is suspected but not yet clearly established. Renal transplant recipients had significant rises of HHV-6 antibodies, and expression of HHV-6 antigens has been found in cases of kidney rejection [27]. In the case of bone marrow transplants, HHV-6 has been found in blood cells, lung and bone marrow samples, and virus detection has been associated with cases of CMV-negative pneumonitis and encephalitis [25,28,29]. In some cases of AIDS-associated retinitis, HHV-6 antigens and DNA have been detected in retina lesions [30] but the role of HHV-6 is unclear, given that CMV was also present in these lesions. Hence, the capacity of HHV-6 to induce disease in immunocompromised patients may be questioned. For these subjects, HHV-6 chronically infects mononuclear blood cells, which are susceptible to being recruited into inflammatory cell infiltrates, and this may act as a confounding factor.

The possible interaction between HHV-6 and HIV-1 remains a matter of debate. Both viruses infect CD4 lymphocytes, and synergistic co-infection has been demonstrated in experimental infections in vitro. Similarly, HHV-6-induced expression of CD4 in CD8-positive cells would provide additional susceptible cells for HIV infection [14]. In vivo, disseminated HHV-6 infections were observed in patients who had died of AIDS [31]. However, many studies addressing either the titer of HHV-6 antibodies or the detection of HHV-6 DNA in body fluids during the course of HIV-1 infection did not support the hypothesis of a synergistic activation between the two viruses [32].

The possible role of HHV-6 in human malignancies has not been proven. Initially, the presence of HHV-6 DNA was demonstrated in tumoral tissue of non-Hodgkin's lymphomas and Hodgkin's disease. However, recent data from studies including samples from control lymphoid tissue did not demonstrate a significantly higher rate of detection in lymphomas than in non-neoplastic lymphoid tissue [12]. Despite initial claims, the involvement of HHV-6 in the pathology of chronic fatigue syndrome [33] or autoimmune diseases such as Sjögren syndrome has not been confirmed. The role of HHV-6 in multiple sclerosis needs further study [34]. Lastly, the capacity of HHV-6 to induce bone marrow suppression has been mentioned with respect to a limited number of cases. This must be compared with the capacity to inhibit bone marrow colony formation observed in vitro with HHV-6 infection [35].

Treatment

Some antiviral agents are efficient against HHV-6 infection in vitro [7]. The pattern of drug susceptibility mimicks that of CMV: HHV-6 is sensitive to ganciclovir and foscarnet, and relatively resistant to acyclovir. No difference in sensitivity was observed between variants A and B. Antiviral chemotherapy has been used in a few cases of HHV-6 infection in bone marrow transplant recipients. However, no controlled study of antiviral efficacy in vivo has been performed and no precise indication for treatment has been defined.

HUMAN HERPESVIRUS 7 (HHV-7)

Virologic properties

The isolation of HHV-7 was first reported in 1990 [36]. The story started as the isolation of a novel strain of HHV-6 from a culture of purified CD4-positive peripheral blood T-lymphocytes obtained from a healthy individual. The cytopathic effects were very similar to those of HHV-6. Electronmicroscopic analyses confirmed the presence of a herpesvirus, but virus DNA did not hybridize with any of the HHV-6 DNA probes tested, and the restriction enzyme pattern

differed widely from that observed for most HHV-6 isolates. This virus was then considered to be a novel human herpesvirus, closely related to HHV-6, and designated as HHV-7. Subsequently, additional isolates of HHV-7 were obtained from saliva and peripheral blood mononuclear cells [37,38].

The HHV-7 structure was found to be very similar to that of HHV-6. HHV-7 DNA exhibited a close genetic relationship with the HHV-6 genome, with a partial homology of about 40% between the two viruses as depicted in preliminary studies [39]. The genomic architecture resembles that of HHV-6, with a long unique region of about 130 kb flanked by two terminal repeats and gene block organization similar to that of HHV-6 [40]. There is no doubt that HHV-7 is a member of the Betaherpesvirinae subfamily.

HHV-7 grows in activated T-cells from peripheral blood or umbilical cord blood [41]. Target cells are quasi-exclusively CD4 positive, and it has been shown that CD4 is an essential component of the cell receptor for HHV-7 [42]. The fact that HIV-1 and HHV-7 share a common pathway of entry into cells might have major implications for the pathology and therapy of HIV infection. HHV-7 infection has been shown to have an inhibitory effect on HIV replication in vitro. Conversely, HIV-1 glycoprotein gp120 exhibited a dose-dependent inhibition of HHV-7 infection. The propagation of HHV-7 in continuous T-cell lines was found to be rather inefficient, while enrichment of mononuclear blood cells for CD4-positive T-cells resulted in an improved virus production after HHV-7 infection.

Epidemiology and diagnosis procedures

The prevalence of HHV-7 infection in the adult population exceeds 90% [43]. Primary infection occurs early in life and it has been suggested that the time of this initial infection was slightly later for HHV-7 than for HHV-6. As with HHV-6, infection is lifelong. HHV-7 is found in saliva with high frequency, probably reflecting the fact that salivary glands comprise a major site of chronic HHV-7 infection [38]. It is therefore believed that saliva is a major route of transmission.

HHV-7 can be isolated from saliva and mononuclear blood cells, but this isolation is rather inefficient when compared with the high frequency of HHV-7 DNA detection, particularly in saliva samples. Culture conditions remain to be improved to increase the rate of isolation. In this context, PCR detection of HHV-7 DNA is the most convenient approach for the diagnosis of HHV-7 infection in body fluids. So far, no distinction between 'latent' and active infection based on PCR results has been published. Several monoclonal antibodies to HHV-7 have been described and may contribute to the direct detection of HHV-7-antigen-expressing cells. Diverse home-made serologic assays starting from HHV-7-infected cells as the source of antigen and using different read-out techniques such as immunofluorescence, immunoblot or ELISA have been published. The main question is the possibility of cross-reactions with either HHV-6 or CMV antibodies.

Clinical manifestations and treatment

So far, no human disease has been clearly linked to HHV-7 infection, except one case of an exanthem subitum-like syndrome associated with primary infection [44]. As with HHV-6, the role of HHV-7 as a cofactor in AIDS as well as an opportunistic agent in infections of immunocompromised people has been discussed but not proven.

In vitro sensitivity of HHV-7 to antiherpetic drugs has not been extensively studied. Preliminary data indicate that HHV-7 infection is inhibited by foscarnet and ganciclovir but not by acyclovir.

HUMAN HERPESVIRUS 8 (HHV-8)

Virologic properties

The causative role of an infectious agent for Kaposi's sarcoma (KS) had been suspected for a long time on the basis of epidemiologic data [45]. The hypothesis of a viral etiology has been mentioned previously [46]. The recent discovery of HHV-8 (also called Kaposi's sarcoma-associated herpesvirus) was founded on a pure molecular biology approach, in contrast with the initial isolation of HHV-6 and HHV-7. Starting from two distinct samples from the same subject, one from a KS lesion and the other from adjacent unaffected tissue, Chang et al. applied representational difference analysis and identified two DNA fragments, 330 and 631 bp long respectively [47]. These fragments were assumed to correspond to the genome of the putative causative agent of KS. These two fragments exhibited homology with the genomic DNA of two viruses, EBV and herpesvirus saimiri (HVS), both members of the Gammaherpesvirinae subfamily. One fragment (330 bp long) encoded a putative protein homologous to capsid proteins of EBV and HSV. Similarly, the second fragment (631 bp long) encoded a putative protein homologous to tegument proteins of EBV and HVS. These homologies were confirmed on larger fragments cloned from genomic DNA banks [48,49] and led to the conclusion that the DNA fragments obtained were part of the genome of a novel herpesvirus.

At present, little is known about the structure of HHV-8 DNA. Preliminary data indicated a size of 270 kbp [50], but more recent analyses tend to demonstrate that this size is indeed close to 140 kb.

Primary sequence analyses of HHV-8 DNA amplified from distinct subjects showed a few changes which indicated some degree of genetic polymorphism [51,52].

In vitro propagation of HHV-8 is very difficult. Following numerous unsuccessful attempts, the virus was ultimately obtained under a cell-free form after chemical induction of a chronically infected cell line [53,54]. This virus-producing cell line, like other chronically infected ones, was derived from a body-cavity-based lymphoma (BCBL). Most of these cell lines also contain EBV DNA sequences, which makes specific analysis of HHV-8 sequences difficult [55]. In vivo target cells for HHV-8 infection include CD19-positive B lymphocytes [56].

Epidemiology and diagnosis procedures

The prevalence of HHV-8 infection in the general population is not yet known, due to the lack of an accessible serologic assay. Two hypotheses must be considered: either HHV-8 infection is present in a small percentage of population, like HSV-2, or HHV-8 infection is widespread and ignored in most cases, as for other human herpesviruses. Both hypotheses are supported by results which, taken together, look conflicting. On the one hand, HHV-8 DNA has not been found frequently, if at all, in the mononuclear blood cells from healthy subjects, and preliminary serologic assays indicate that specific HHV-8 antibodies are detected only in patients with KS or at risk of developing KS [48]. On the other hand, HHV-8 DNA has been found in sperm [57] and lymph nodes of numerous people who were healthy or not at risk of KS. However, it is possible that the prevalence of HHV-8 infection differs according to ethnic group or geographic area.

The route of virus transmission is unknown. Because the putative infectious agent responsible for KS was suspected to be transmitted by sexual contact, it has been hypothesized that this would be the case for HHV-8, but no definite proof has yet been provided. The virus is not frequently found in saliva. Some authors have reported a high detection frequency in sperm from both homosexual men (91% of samples) and healthy donors (23% of samples), but these results [57] are controversial. In most reports, the presence of HHV-8 DNA sequences in blood cells is restricted to patients with HHV-8-associated disease (see below).

Since the initial description of HHV-8, detection of HHV-8 infection has been done by means of PCR [47,51,52]. This has permitted the demonstration of the presence of the virus in tissue lesions as well as in normal human tissues. Isolation and serial propagation of the virus in vitro has not been clearly achieved so far using conventional lymphocyte cultures. Serologic assays are currently under development. An immunofluorescence assay using a chronically infected cell line as an antigen has been described and provided evidence that KS patients have higher HHV-8 antibody titers than controls [48]. However, due to the concomitant presence of EBV in the cell line, the preliminary adsorption of serum EBV antibodies on EBV-infected cell lines is required. Preliminary results have been reported using immunoblot assays. The prevalence of HHV-8 infection with one of these immunoblot assays is 77.5% among HIV-positive subjects with KS, 17.5% among control HIV-positive subjects, and 0% among healthy blood donors (P. Moore, personal communication), some very interesting data which deserve further investigation.

Clinical manifestations and therapy

HHV-8 infection has been associated with all forms of KS: AIDS-associated KS, classical or Mediterranean KS, endemic or African KS, and post-transplant KS [58–65]. Virus is detected in nearly 100% of tissue lesions. Virus is also present in adjacent normal skin [59] and in peripheral blood mononuclear cells from KS patients [52,58], but with a lower frequency and/or level than in KS lesions. Prior to the occurrence of KS, the detection of HHV-8 in blood cells is predictive of the disease. In situ PCR has shown that HHV-8 DNA was present in the nucleus of endothelial and spindle cells within the tumor [66,67]. Surprisingly, the virus is not detected any longer within continuous cell cultures derived from KS lesions [61].

HHV-8 is also detected in BCBL [68–70] and virus load is very high, ranging from 40 up to 80 copies of virus genome per cell. This high virus load permitted the detection of HHV-8 DNA not only by means of PCR but also by means of Southern hybridization. These findings are in contrast with those obtained for other forms of non-Hodgkin's lymphomas: both detection rate and virus load are much lower than for BCBL [71] (unpublished results).

Castleman's disease, a lymphoid tissue disease characterized by polyclonal lymphoid proliferation and vascular hyperplasia, is associated with HHV-8 infection [72–74] in both HIV-positive and HIV-negative individuals. The virus is detected in lymph node biopsies, and mononuclear blood cells.

It is not yet possible to have a clear picture of the role of HHV-8 in the three diseases mentioned above. HHV-8 belongs to the Gammaherpesvirinae subfamily, some members of which, such as EBV and HVS, are involved in oncogenesis processes. It is tempting to

conclude that HHV-8, a B-lymphotropic herpesvirus, is responsible for lymphoid tissue proliferation and KS. However, a simple role of passenger virus for HHV-8, the multiplication of which would be promoted in the context of lymphoid tissue diseases, cannot be ruled out.

The characterization of the pathogenic role of HHV-8 deserves further study and will probably require numerous investigations. A possible approach is the study of antiherpetic drug effects on HHV-8-associated diseases. The study of the effects of foscarnet on KS has provided conflicting results [75–77]. However, the report of KS tumor remission following foscarnet therapy must be considered.

FUTURE PERSPECTIVES FOR NOVEL HERPESVIRUSES

The recent description of three novel human herpesviruses undoubtly opens new avenues for medical virology. It is surprising to observe that HHV-6 and HHV-7, two viruses which, taken together, infect 100% of the adult population, were still unknown 10 years ago. The question of the prevalence of HHV-8 is being investigated and will focus medical attention in the next months. The most recent data strongly suggest that HHV-8 is not ubiquitous, at least in the populations of Western countries [78,79]. These viruses are in search of their pathology and, again, most research efforts in the near future will probably concentrate on HHV-8, because of the seriousness of potentially associated diseases. An additional reason for developing research on novel herpesviruses concerns efficient antiviral therapy. A wide set of antiherpetic drugs is now available in clinical settings, and some others are in development with good prospects of efficient medical use. It would be a pity to miss this opportunity of therapy if the causative role of novel herpesviruses in serious diseases is clearly demonstrated.

Lastly, lymphotropism is a common property shared by novel herpesviruses. The possibility of interactions between these viruses and other viruses infecting lymphoid tissue, such as HIV, raises the hope of a better understanding of immune dysfunctions. This pathway of investigation cannot be neglected, since, if necessary, specific therapy appears to be a reasonable goal. In addition, the use of viral vectors derived from these novel herpesviruses and targeted to special populations of lymphocytes could constitute the basis of attractive projects.

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